ANTI-DR5 ANTIBODIES AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional of U.S. patent application Ser. No. 16/451,714, filed Jun. 25, 2019 (now U.S. Pat. No. 10,882,913), which is a continuation of U.S. patent application Ser. No. 15/780,268, filed May 31, 2018, which is a 35 U.S.C. 371 national stage filing of International Application No. PCT/EP2016/079518, filed Dec. 1, 2016, which claims the benefit of Danish Patent Application Nos. PA 2015 00771, filed Dec. 1, 2015, PA 2015 00787, filed Dec. 7, 2015, PA 2015 00788, filed Dec. 7, 2015, PA 2016 00701, filed Nov. 10, 2016, and PA 2016 00702, filed Nov. 10, 2016. The contents of the aforementioned applications are hereby incorporated by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Dec. 1, 2020, is named GMI_169 AUSCNDV_Sequence_Listing.txt and is 144,220 bytes in size.

FIELD OF THE INVENTION

[0003] The present invention relates to monospecific or bispecific antibody molecules that specifically bind the human DR5 antigen. The invention relates in particular to DR5-specific antibody molecules of the IgG1 isotype having a mutation in the Fc region that enhances clustering of IgG molecules after cell—surface antigen binding. The invention further relates to a combination of antibody molecules binding different epitopes on human DR5. The invention also relates to pharmaceutical compositions containing these molecules and the treatment of cancer and other diseases using these compositions.

BACKGROUND OF THE INVENTION

[0004] DR5, also known as death receptor 5, Tumor necrosis factor receptor superfamily member 10B, TNFRSF10B, TNF-related apoptosis-inducing ligand receptor 2, TRAIL receptor 2, TRAIL-R2 and CD262, is a cell surface receptor of the TNF receptor superfamily that binds tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and mediates apoptosis. DR5 is a single-pass type I membrane protein with three extracellular cysteine-rich domains (CRDs), a transmembrane domain (TM) and a cytoplasmic domain containing a death domain (DD). In the absence of ligand, DR5 exists in the cell membrane either as monomer or as pre-assembled complexes of two or three receptors through interactions of the first cysteine-rich domain, also known as pre-ligand assembly domain (PLAD) (Wassenaar et al., Proteins. 2008 Feb. 1; 70(2):333-43; Valley et al., J Biol Chem. 2012 Jun. 15; 287(25):21265-78; Sessler et al., Pharmacol Ther. 2013 November; 140(2):186-99). A Crystal structure of TRAIL in complex with the DR5 ectodomain showed that TRAIL binds to CRD2 and CRD3 in the extracellular domain of DR5 in a complex containing a trimeric receptor and a trimeric ligand (Hymowitz et al., Mol Cell. 1999 October; 4(4):563-71). The DR5 trimers can further cluster into higher-order receptor aggregates in lipid macrodomains, so-called lipid rafts (Sessler et al., Pharmacol Ther. 2013 November; 140(2):186-99). In the ligand-bound conformation, the cytoplasmic death domain-containing adaptor protein FADD associate with the intracellular DD surface of the oligomerized DR5 molecules and engage initiator caspases caspase-8 and caspase-10 to form the death-inducing signaling complex (DISC).

[0005] Based on the sensitivity of cancer cells to TRAIL-mediated apoptosis, numerous agents were developed to activate this pathway to induce apoptosis selectively in cancer cells. Human recombinant TRAIL (hrTRAIL), is being developed as dulanermin, and a series of conventional (monospecific, bivalent) anti-DR5 antibodies have been developed and tested in the clinic (reviewed in Ashkenazi et al., Nat Rev Drug Discov. 2008 December; 7(12):1001-12; Trivedi et al., Front Oncol. 2015 Apr. 2; 5:69): DR5 antibodies include lexatumumab (HGS-ETR2), HGS-TR2J, conatumumab (AMG655), tigatuzumab (CS-1008), drozitumab (Apomab) and LBY-135. Clinical studies with these compounds demonstrated that DR5 antibodies were generally well tolerated but failed to show convincing and significant clinical benefit. Efforts to enhance the efficacy of DR5 targeting antibodies mainly focus on (i) improving the sensitivity of cancer cells to DR5 agonists through combination treatment, (ii) developing biomarkers for better patient stratification, and (iii) the development of DR5-targeting agents that activate DR5 signaling and apoptosis-induction more effectively (reviewed in Lim et al., Expert Opin Ther Targets. 2015 May 25:1-15; Twomey et al., Drug Resist Updat. 2015 March; 19:13-21; Reddy et al., PLoS One. 2015 Sep. 17; 10(9)). Different therapeutic formats for increasing DR5 activation have been described and include oligomerization of synthetic DR5 binding peptides, linear fusions of DR5-specific scaffolds, nanoparticle-based delivery systems of rhTRAIL or conatumumab and multivalent DR5 antibody-based formats (reviewed in Holland et al., Cytokine Growth Factor Rev. 2014 Apr.; 25(2):185-93). APG880 and derivatives exist of two single chain TRAIL receptor binding (scTRAIL-RBD) molecules (TRAIL mimics) fused to the Fc part of a human IgG. Each scTRAIL-RBD has three receptor binding sites resulting in a hexavalent binding mode in the fusion protein (WO 2010/003766 A2). A prototype scTRAIL-RBD (APG350) has been described to induce FcγR-independent antitumor efficacy in vivo (Gieffers et al., Mol Cancer Ther, 2013. 12(12): p. 2735-47). A tetravalent anti-DR5 antibody fragment-derived construct, assembled by fusion of an anti-DR5 scFv fragment, human serum albumin residues and the tetramerization domain of human p53, has been shown to induce apoptosis more potently than the monovalent construct (Liu et al., Biomed Pharmacother. 2015 March; 70:41-5). Nanobody molecules are single domain antibody fragments (VHH) derived from camelid heavy chain-only antibodies, which, similarly to scFvs, can be linked to form multivalent molecules. Preclinical in vitro studies showed that TAS266, a tetravalent anti-DR5 Nanobody® molecule, was more potent than TRAIL or crosslinked DR5 antibody LBY-135, which was attributed to more rapid caspase activation kinetics (Huet et al., MAbs. 2014; 6(6):1560-70). TAS266 was also more potent in vivo than the parental murine mAb of LBY-135. MultYbody™ molecules (MultYmab technology) are based on the fusion of a homomultimerizing peptide to the Fc of one heavy chains in an IgG heterodimer (knob into hole), making MultYbody molecules intrinsically multiva-